Responsible regulation in action? Responsible research and innovation and the European Bank for induced pluripotent stem cells

Responsible Regulation in Action?
Responsible Research and Innovation and the European Bank for induced pluripotent Stem Cells

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Abstract: Ambitions for regenerative medicine remains a strong motivator for healthcare research and resource development. Central to the evolving vision for regenerative medicine are stem cells, and now human induced pluripotent stem cells (iPSCs). Against the promissory and technically innovative backdrop of this technology, there has been a growing concern for legitimacy and integrity in science and innovation. This, in turn, has encouraged discourses around the idea of 'responsibility', and the notion of 'responsible research and innovation' (RRI), which has gained considerable policy traction in Europe. This paper considers the concept of RRI within the context of a specific European research project: the European Bank for induced pluripotent Stem Cells (EBiSC). EBiSC is a resource development project – a biobank – that has as its stated aims the establishment of a leading European-based bank that will, inter alia, promote wider use of iPSCs and global iPSC banking with the ultimate aim of enhancing the health of people. Specifically, this paper considers how EBiSC's Phase I (2014-2016) governance activities comply with expectations that might be distilled from RRI, and what RRI might impose on EBiSC's post-Phase II (2017-2019) entity. In doing so, it offers some guidance on how RRI might be operationalised at the project level.

Keywords: European Union; Responsible Research and Innovation; science governance; induced pluripotent stem cells; biobanks; EBiSC; values

1. Introduction

Very broadly, 'regulation' is meant to be a framework for decision-making that ensures a focused, structured, and ongoing attempt at steering conduct. It is:

> the sustained and focused attempt to alter the behaviour of others according to standards or goals with the intention of producing a broadly identified outcome or outcomes, which may involve mechanisms of standard-setting, information gathering, and behaviour-modification.[1]

Given this understanding, regulation typically follows a cycle of 'direction, detection, and correction', relying on signals that are meant to direct the conduct of regulatees, methods of monitoring the conduct of regulatees, and measures aimed at correcting that conduct where there is deviation from established standards.[2] Further, although 'responsible regulation' might start with risk and safety concerns, it does not end there; in the context of new technologies and practices, like population biobanking, it involves attention to multiple issues, such as how the technology/practice distributes risk and benefit, what social and political arrangements are necessary for, and favoured by, the technology/practice, and what the real purposes of the technology/practice are.[3]

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1 J Black, 'What is Regulatory Innovation?' in J Black, M Lodge and M Thatcher (eds.), *Regulatory Innovation* (Cheltenham: Edward Elgar, 2005) 1-X, at 11.

2 R Brownsword, 'Responsible Regulation: Prudence, Precaution and Stewardship' (2011) 62 N Ir Legal Q. 573.

3 M Lee, 'Beyond Safety? The Broadening Scope of Risk Regulation' (2009) 62 Current Legal Problems 242.

It has additionally been observed that lawyers often make the mistake of trying to understand the governance of the social world through legal instruments.[4] However, good governance is often enacted by many parties, including those who are themselves governed. Thus, regulatees also construct the governance setting applicable to them. In Europe, the idea of 'good governance' of research and innovation is presently influenced by the idea of 'responsibility', and the notion of 'responsible research and innovation' (RRI). In fact, RRI has gained considerable policy traction in Europe. It was mooted in the Proposal for a Regulation Establishing Horizon 2020,[5] and then included in the Regulation itself. Recital 22 of Regulation (EU) No. 1291/2013 of the European Parliament and of the Council of 11 December 2013 establishing Horizon 2020 states:

> With the aim of deepening the relationship between science and society and reinforcing public confidence in science, Horizon 2020 should foster the informed engagement of citizens and civil society in research and innovation matters by … *developing responsible research and innovation agendas that meet citizens' and civil society's concerns and expectations* and by facilitating their participation in Horizon 2020 activities. The engagement of citizens and civil society should be coupled with public outreach activities to generate and sustain public support for Horizon 2020. [emphasis added]

In *Work Programme 2014-2015: Science with and for Society*, implemented by Decision C(2015)2453 of 17 April 2015 of the European Commission (EC), RRI-related projects were included for funding.[6]

In this paper, I consider RRI as a regulatory concept that imposes on regulatees obligations associated with 'direction, detection, and correction'. In doing so, I focus on a specific European research project: the European Bank for induced pluripotent Stem Cells (EBiSC).[7] Funded by the EC's Innovative Medicines Initiative Joint Undertaking (IMI-JU) with the European Federation of Pharmaceutical Industries and Associations (EFPIA), EBiSC is a resource development project – a biobank – that has as its stated aims the establishment of a sustainable bank for induced pluripotent stem cells (iPSCs).[8] Indeed, it is expected that EBiSC will:[9]

- promote wider use of iPSCs and encourage global iPSC banking with the ultimate aim of enhancing the health of people and contributing to the development of the bioeconomy;
- spearhead Europe in iPSC banking by forging collaborative links internationally; and
- become a flagship enterprise by setting new technical standards and best practice.

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4 Brownsword, note 2.

5 European Commission, *Establishing Horizon 2020 – The Framework Programme for Research and Innovation (2014-2020)*, COM(2011) 809 Final.

6 European Commission, *Horizon 2020 Work Programme 2014-2015: Science with and for Society (Revised)*, EC Decision C(2015)2453; European Commission, at http://ec.europa.eu/programmes/horizon2020/en/h2020-section/responsible-research-innovation [accessed 20 April 2017].

7 The EBiSC project has received support from the Innovative Medicines Initiative Joint Undertaking (Agreement n° 115582), a scheme whereby the project receives a financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013), and financial and/or in-kind contributions from the European Federation of Pharmaceutical Industries and Associations.

8 iPSCs are tissue or organ-derived cells that have been reprogrammed to an embryonic stem cell-like state by being forced to express genes and factors important for maintaining the defining properties of embryonic stem cells. A key feature of pluripotent stem cells is their ability to be propagated indefinitely whilst maintaining stable properties in tissue culture. See K Takahashi, K Tanabe et al., 'Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors' (2007) 131 Cell 861. With the advent of iPSCs, research opportunities have expanded dramatically: Organization for Economic Cooperation and Development, *The Bioeconomy to 2030: Designing a Policy Agenda* (Paris: OECD, 2009; G Vogel, 'Cellular Reprogramming: new Technique RiPS Open Stem Cell Field' (2010) 330 Science 162.

9 See EBiSC, at http://www.ebisc.org/about-ebisc/the-project.php.

This paper considers how EBiSC's Phase I (2014-2016) governance activities comply with expectations that might be distilled from the regulatory concept of RRI, and what RRI might impose on EBiSC's post-Phase II (2017-2019) structures (i.e., its Legacy Entity). In doing so, it offers some guidance on how this regulatory concept might be operationalised at the project (or regulatee) level. As such, in the second and third sections below, I explore the idea of RRI generally, and then what it might impose on those working in the research setting, with a view to articulating a framework for evaluating a project like EBiSC. In the fourth section, I apply that framework to EBiSC's Phase I structures and practices, which were aimed not only at founding an efficient and reliable resource, but also a legally and ethically responsible one. Given the ambitions for EBiSC, in the final section I offer a view on what RRI might additionally impose with respect to governance of the Legacy Entity in the post-Phase II (2017-2019) period. I conclude that, if projects like EBiSC, which are meant to endure into the future, are to avoid governance failures, and remain legitimate, they will need to pay sufficient attention to the matters raised.

2. The Meaning of RRI

RRI evolved out of discussions about research integrity in relation to controversial technologies like genomics, synthetic biology, and nanotechnologies,[10] and from concerns about the value of science,[11] the control of technologies in contexts of uncertainty and ignorance,[12] and the impact of globalism.[13] One of the aims was to prevent technological disasters such as have been suffered in the past.[14] It should be clear from this genesis that RRI is meant to help protect individuals and communities, and to encourage public support for science and innovation. On the latter, RRI is not about instilling trust as a means of assuring the scientific undertaking – and one might argue that it is only marginally within the power of protagonists to induce feelings of trust in others – but rather about demonstrating to stakeholders the trustworthiness of primary actors, and so to encourage relations of trust.[15] On the former, RRI is concerned with facilitating the internalisation of justice-enhancing characteristics such as autonomy, equity, and democracy. These are particularly pertinent where undertakings are supported by public funds, obtain resources through the altruism of others, and aim to serve human wellbeing in contexts where a lack of justice can have harmful consequences for actors beyond the immediate undertaking.[16]

With respect to a working definition, RRI has been described as advancing the idea of adaptive and anticipatory governance (i.e., that it is, at base, oriented towards anticipation, responsiveness, reflexivity, and inclusiveness).[17] It has also been argued that, like some of the earlier science governance frameworks,

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10 B Adam and G Groves, 'Futures Tended: Care and Future-Oriented Responsibility' (2011) 31 Bulletin of Science, Technology & Society 17-27; R Von Schomberg (ed.), *Toward Responsible Research and Innovation in the ICTs and Security Technologies Fields* (Brussels: European Commission, 2011).

11 M Kearnes and M Weinroth, *A New Mandate? Research Policy in a Technological Society* (Durham: DUP, 2011).

12 D Collingridge, *The Social Control of Technology* (London: Pinter, 1980).

13 D Wright, et al., 'Precaution and Privacy Impact Assessment as Modes towards Risk Governance' in Von Schomberg (ed.), note 10, 83-97.

14 H Sutcliffe, *A Report on Responsible Research and Innovation* (2011), at https://ec.europa.eu/research/science-society/document_library/pdf_06/rri-report-hilary-sutcliffe_en.pdf [accessed 22 October 2015].

15 O O'Neill, *Autonomy and Trust in Bioethics* (Cambridge: CUP, 2002); N Manson and O O'Neill, *Rethinking Informed Consent in Bioethics* (Cambridge: CUP, 2007).

16 It is well known that critical shortfalls in trust and/or perceptions of justice can lead not only to failure of the undertaking, but also, as demonstrated by a variety of healthcare and research missteps, to other and very public consequences: M Hunter, 'Medical research under threat after Alder Hey scandal' (2001) 322 British Medical Journal 448; M Hansson, 'Ethics and Biobanks' (2009) 100 British J Cancer 8; J Higgins, 'Hospitals in Trouble' in M Exworthy et al. (eds.), *Shaping Health Policy* (Bristol: Policy Press, 2012) 95.

17 Von Schomberg, note 10; R Owen and N Goldberg, 'Responsible Innovation: A Pilot Study with the UK Engineering and Physical Sciences Research Council' (2010) 30 Risk Analysis 1699; R Owen, P Macnaghten and J Stilgoe, 'Responsible Research and Innovation: From Science in Society to Science for Society, with Society' (2012) 39 Science &

RRI strives for a more democratic and equitable science/society relationship, one that is deliberative and cooperative rather than competitive and bargained.[18] Sutcliffe argues that RRI means that science and innovation activities must: focus on achieving public goods, particularly sustainable social and environmental benefits; be assessed in part on how well they facilitate positive social, ethical, and environmental impacts; and integrate ongoing dialogue with communities of interest, including public and non-governmental organisations.[19] Ultimately, RRI calls for a comprehensive approach to research whereby all stakeholders can, at an early stage, develop insight into the consequences of research outcomes, secure knowledge about the range of options appropriate to a problem, effectively assess those options and outcomes in terms of social needs and moral values, and use this information to design new research, products, and services.[20]

RRI now serves as a cross-cutting theme for the EU's Horizon 2020 Programme for Research and Innovation. Article 12(1) of Regulation (EU) No 1291/2013, states that, in addition to advice and inputs provided by independent experts set up by the EC, inputs will be provided from dialogue structures created under international science and technology agreements, forward-looking activities, targeted public consultations, and transparent and interactive processes that ensure that responsible research and innovation is supported. On its RRI Toolkit Page, the EC states that RRI is about involving society upstream in the research process so as to align outcomes with societal values.[21] It also states that RRI calls for public engagement, open access, gender equality, science education, ethics, and governance. On its Horizon 2020 Page, the EC defines RRI as follows:

> Responsible research and innovation is an approach that anticipates and assesses potential implications and societal expectations with regard to research and innovation, with the aim to foster the design of inclusive and sustainable research and innovation.
>
> Responsible Research and Innovation (RRI) implies that societal actors (researchers, citizens, policy makers, business, third sector organisations, etc.) work together during the whole research and innovation process in order to better align both the process and its outcomes with the values, needs and expectations of society.[22]

The EC goes on to state that RRI necessitates engaging actors in inclusive, participatory practices at all stages of research and all levels of governance, from agenda setting, to design and implementation, to evaluation. Perceived benefits are articulated as informed and engaged publics, responsible actors and institutions, ethically acceptable sustainable research and practices, and solutions to major societal challenges.

Given the above, it seems clear that RRI should be understood as having two components. Its first, a substantive component, provides a normative foundation for science and innovation. This includes the idea of collective responsibility and collaborative trajectory-formation, the foregrounding and evolutionary development of a research ethos or culture, and the explicit imperative that research outcomes tackle

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Public Policy 751; B Stahl, 'Responsible Research and Innovation: The Role of Privacy in an Emerging Framework' (2013) 40 Science & Public Policy 708.

18 M Van Oudheusden, 'Where are the politics in responsible innovation? European governance, technology assessment, and beyond' (2014) 1 J Responsible Innovation 67.

19 Sutcliffe, note 14.

20 EC Expert Group on Dealing with Ethical and Regulatory Challenges of International Biobank Research, *Biobanks for Europe: A Challenge for Governance* (Brussels: EC, 2012); EC Expert Group on the State of the Art in Europe on Responsible Research and Innovation, *Options for Strengthening Responsible Research and Innovation* (Brussels: EC, 2013).

21 EU, *RRI Toolkit* (2017), at https://www.rri-tools.eu/about-rri [accessed 8 March 2017].

22 EU, *Horizon 2020: Responsible Research and Innovation* (2017), at http://ec.europa.eu/programmes/horizon2020/en/h2020-section/responsible-research-innovation [accessed 7 March 2017].

societal challenges, contribute to sustainable development, and exhibit ethical acceptability.[23] The second component is a procedural component, which demands the construction and maintenance of inclusive and discursive decision-making processes aimed at broadening governance participation and expanding governance considerations to include anticipation and foresighting. This understanding of RRI builds on earlier scholarship aimed at opening up new and emerging science and technologies to public debate and reflection, and on persistent calls for actors and communities of interest to become mutually responsive to each other, forming governance partnerships that might better realise the promises being made on behalf of new lines of inquiry, techniques, and technologies.

3. The Demands of RRI on Individual Projects

Obviously, RRI imposes obligations on governments, regulators, and funders, for they set social objectives and technical targets for innovation (and the funding of same). And one can already see a range of actions that have been taken by these bodies to operationalise the idea of RRI. For example, the UK's Engineering and Physical Sciences Research Council has begun to reposition itself as a 'sponsor' and 'shaper' of research, and has tried to ensure responsible actions in the face of ignorance, uncertainty and ambiguity,[24] recently announcing its commitment to an RRI framework.[25] Similarly, through the crafting of the call to which EBiSC responded, and the vetting of the applications, the IMI has taken into account some of the objectives of RRI, ensuring that proposed activities reflect, to the extent possible given scientific objectives and budgets, concepts derivative of RRI.[26] In this way, the notion of RRI reaches through to researchers and imposes obligations on them to shape their activities according to appropriate norms.[27]

But what does RRI mean for projects like EBiSC which are primarily instrumental and understood as in some way advancing policy positions that have already been determined? While some of the most demanding engagement and anticipatory activities may have already taken place, the central concept of 'responsibility', which is both morally and practically significant, remains an objective that other actors must pursue (and achieve) within projects, particularly biobank projects like EBiSC which are expected to continue operating beyond the funding period. Attention to responsibility demands that research activities not only be compliant with fundamental human rights (attending to safety and efficacy in the process), but also that they incorporate a sufficient level of clarity, attention to standards, accountability, reflection, and democracy.[28] Indeed, the Nuffield Council on Bioethics has stated that the duty to develop emerging biotechnologies in accordance with the public interest and pursuant to a public ethic falls not only on public authorities, but also, as a matter of moral responsibility, on firms, groups and individuals.[29] It goes on to offer some procedural virtues intended to foster a public discourse ethics, including openness and inclusion, accountability, public reasoning, candour, enablement, and caution.[30]

From the above definitions, one can distil a number of RRI-sensitive operational expectations relevant to an international biobanking undertaking like EBiSC, namely that the biobank will:

i. pursue salutary knowledge and healthcare objectives, and communicate both them and information about the operations of the undertaking to the public;

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[23] For more on this component of RRI, see S Harmon, 'Responsible Research and Innovation: Function, Form, Failings and Contribution to Good Governance of Individual Projects' in review with the J Responsible Innovation.

[24] R Owen, 'The UK Engineering and Physical Sciences Research Council's commitment to a framework for responsible innovation' (2014) 1 J Responsible Innovation 113-117.

[25] EPSRC, *Framework for Responsible Innovation*, at https://www.epsrc.ac.uk/research/framework/ [accessed 23 October 2015].

[26] For more on IMI and its calls, see https://www.imi.europa.eu/content/documents [accessed 27 April 2017].

[27] Owen et al., note 17.

[28] Ibid; Stahl, note 17.

[29] Nuffield Council on Bioethics, *Emerging Biotechnologies: Technology, Choice and the Public Good* (London: NCOB, 2012), at 67.

[30] Ibid, Ch. 4.

ii. approach operational issues (i.e., key scientific and practical demands) in a way that is ethically defensible; and

iii. design-in governance elements that make clear responsibilities, recourse for those wronged/harmed, and avenues for engagement by stakeholders with regard to changing conditions, risks, operational possibilities, etc., bearing in mind the virtues offered by the Nuffield Council on Bioethics for ensuring that questions of value and conduct are raised and addressed.

The extent to which the project (and resultant Legacy Entity) reflects these criteria offers some indication about the extent to which RRI is being achieved.

4. The RRI Criteria and EBiSC Phase I

EBiSC Phase I (2014-2016) was structured by the Project Agreement (Agreement), the Description of Work (DOW), and the documents developed iteratively against the background of the 'hot start',[31] being the Common Information Pamphlet (CIP), the Common Consent Form (CCF), the Material Deposit Agreement (MDA), and Access and User Agreements (AUA).[32] These documents serve as the primary means of structuring EBiSC's internal activities and external relations and decisional processes.

i. Salutary Health Objectives and Operations Clearly Communicated

The first RRI-alignment criteria is that objectives should be justifiable (i.e., should represent a 'good outcome'), and both objectives and their supporting operations should be made abundantly clear to publics. In other words, EBiSC must sufficiently expose its (socially useful and ethically sound) ambitions and operations to public scrutiny. This involves communication of aims and operations, but also a justification of same according to values and some defensible sense of public good.

Human ESCs have proven to be controversial, with concerns revolving around moral, technical and political issues.[33] Those relating to personhood, dignity and instrumentalisation have been particularly divisive.[34] Thus, iPSCs were welcomed as a technically promising and less morally troubling route toward

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[31] Under the 'hot start', pre-existing samples and iPSC lines obtained for a range of purposes and under variable conditions by different members or associated organisations were brought into the bank, while processes were still being designed and new lines were being commissioned. The idea was that the bank would be 'open for business' by the end of Phase I: P De Sousa, R Steeg et al., 'Rapid establishment of the European Bank for induced Pluripotent Stem Cells (EBiSC)-the Hot Start experience' (2017) 20 Stem Cell Research 105.

[32] These forms, and the SOPs they represent, are under constant scrutiny, and are subject to regular revision. The versions to which this paper refers were in effect as of 1 November 2016.

[33] For example, there have been persistent expressions of uncertainty about the scope of the term 'human', the moral status of the embryo, and the appropriate/actual beginning of personhood, and concern around the safety of female embryo donors, who are often medicinally super-ovulated to produce sufficient or excess embryos. The justifiability of hESC acquisition, which requires the destruction of early embryos, has resulted in significant controversy and made internationally harmonised approaches to hESC impossible. Similarly, questions have been asked about the propriety of investing large sums of finite research resources into expensive technologies that have little potential to reach the clinic in the short term, and might, in any event, prove inaccessible to large segments of the population, both locally and globally.

[34] For more on the promise and controversies, see S Harmon and A Bruce, 'Discursive Typologies and Moral Values in Stem Cell Politics, Regulation and Commercialisation: Some Preliminary Observations' (2009) 6 J International Biotechnology Law 61 (Part I) and 89 (Part II). For a discussion of the different regulatory positions relating to hESCs, see S Harmon, 'Semantic, Pedantic or Paradigm Shift? Recruitment, Retention and Property in Modern Population Biobanking' (2008) 16 European J Health Law 27. The view that such use is contrary to human dignity came before the European Court of Justice in *Brüstle v Greenpeace eV*, Case C-34/10, 18 October 2011, Grand Chamber. For more on

clinical regenerative medicine (and the IMI-JU entertained funding proposals for iPSC-related projects).[35]

While EBiSC fails to acknowledge this history, it does identify a number of preclinical uses and potential benefits, including:[36]

- better understandings of the mechanism of cellular reprogramming, factors determining pluripotency, and the programmed nature of individual cell fates;

- better understandings of the genetic basis of disease, how individual patients within a given diagnosis are different, the development of new medicines as future treatments for those diagnoses, and support for clinical understanding of individual patient responses to medicines being tested;

- development of disease-representative cell lines differentiated into relevant tissue types such that they can be used in phenotypic screens to identify compounds that cause a desirable change in phenotype, thereby offering prospects in symptom or disease modification;

- validation of biochemical pathway targets that have been previously hypothesized as potentially disease-modifying, thereby leading to a higher probability of drug efficacy in clinical development;

- identification of individuals' diseases at the molecular level so that targeted treatments can be deployed, a course based on the ability to better stratify into more precise treatment groups those patients who have been given a particular diagnosis.; and

- use in pharmacovigilance once medicines have been approved for market, by providing a cell-based assay to identify the molecular correlation of individual patient response variations to a given drug.[37]

And of course, ambitions for this technology being used in a stratified or personalised clinical context remain largely intact, though they have been pushed well down the pipeline.

EBiSC assumes, without explicitly stating, that these potential outcomes are socially useful and worthy of investment. To achieve them, it was felt that a consistent supply of ethically sourced, standardised, high-quality iPSC lines is needed, and if potentially crippling inefficiencies are to be avoided, such will have to be supplied by internationally networked collaborative banks like EBiSC. Thus, EBiSC self-describes as a response to increasing researcher demand for quality-controlled, disease-relevant research grade iPSC lines.[38] With extended funding, EBiSC is expected to become a self-sustaining bank by 2019, boasting a catalogue capacity of 10,000 cell lines. That Legacy Entity will, it is expected, be a centralised European not-for-profit iPSC bank providing all qualified users with access to top-quality, scalable, cost-efficient and customised products from a large online catalogue.

This general vision for iPSC use in research is articulated in the DOW.[39] The Agreement states that

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this case, see S Harmon, G Laurie and A Courtney, 'Dignity, Plurality and Patentability: The Unfinished Story of Brüstle v Greenpeace' (2012) 38 European Law Rev 92.

35 Though it should be acknowledged that extensive research is required to understand how to use iPSCs safely and effectively in the clinical setting, and privacy concerns persist because of the traceability of samples: M Morrison, L Moraia and J Steele, 'Traceability in stem cell research: From participant sample to induced pluripotent stem cell and back' (2016) 11 Regenerative Medicine 73.

36 EBiSC, *Major Applications of iPSC* (2017), at https://www.ebisc.org/the-ebisc-catalogue/major-applications-of-ipsc.php [accessed 27 April 2017].

37 And such pharmacovigilance is expected under medicinal products regulation, but it is also rarely effectively or systematically pursued: P Fontanarosa, D Rennie et al., 'Postmarketing Surveillance—Lack of Vigilance, Lack of Trust' (2003) 292 JAMA 2647; P Waller, 'Getting to grips with the new European Union pharmacovigilance legislation' (2011) 20 Pharma & Drug Safety 544.

38 De Sousa et al., note 31.

39 DOW, at 8.

EBiSC accedes to the ethical framework of FP7, and all existing and future applicable legislation, and will refrain from pursuing (under this project) research aimed at human cloning for reproductive purposes, modifying the heritable or germline genetic heritage of human beings (through, for example, gene editing technologies),[40] and creating human embryos solely for research or SC procurement.[41] These are important commitments, but these documents are not publicly available. So how are EBiSC's justifications and objective communicated?

The answer is that they are communicated through direct interactions with Members, through flyers distributed, and presentations made, at expert events, and more generally and consistently through EBiSC's website, which is the primary public-facing tool for communication. It states that EBiSC aims to establish a European Bank for iPSCs in support of preclinical research and in response to increasing demands for quality-controlled, disease-relevant, research-grade iPSC lines, data and cell services. Its perceived benefits and intended scope, together with the general structure of the project are conveyed in the Home, About EBiSC, Catalogue, and Partners pages. Perhaps the most informative communique on the website is the General Project Presentation (GPP), which positions iPSCs and EBiSC in the research environment, identifies some Phase I milestones and benefits to stakeholders, and defends its aims by claiming that a central resource will:

1. define and disseminate best practice for iPSC-based research to donors, clinicians, funders, patients, and researchers;
2. provide confidence in current European practice for iPSC research;
3. provide a focal point for academics and SME's for technology innovation; and
4. enable faster, more cost-effective research.

Of course, the validity of some of EBiSC's claims and expectations has yet to be proven, and the website is undeniably aimed at target communities (e.g., potential depositors and potential users), as demonstrated by the range of documents on the Documentation page. Further, while the GPP is informative, it is not strongly foregrounded in the website. Buried on the Documentation page (where one might rather expect to see the CIP, CFF, MDA, and AUA), it probably does not meet the strong signalling/communication function called for by RRI. Ultimately, then, the website conveys the sense of commitment held by the Members together with some understanding of the project's general structure and activities, but the detail required to emphatically meet the demands of RRI is absent.

ii. Operational Challenges Ethically Managed

A project of this size and diffusion poses a number of operational challenges, many characterised by uncertainty and requiring substantial and sustained support, specialised infrastructure, and technical competence.[42] While operational challenges will have scientific foundations, they are also undeniably moral in nature, and they speak to the ethical grounding of the project.[43] For example, ensuring the availability of quality lines and associated data, a practical aim grounded in science and technical capabilities, has the ethically significant objective of reducing the expense and labour of collecting human material and the need

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[40] For more on these, see J Doudna and E Charpentier, 'The New Frontier of Genome Engineering with CRISPR-Cas9' (2014) 346 Science 1077, and J Sugarman, 'Ethics and Germline Gene Editing' (2015) 16 EMBO Reports 879.

[41] Agreement, Special Clause 5.

[42] M Turner, S Leslie et al., 'Toward the Development of a Global Induced Pluripotent Stem Cell Library' (2013) 13 Cell Stem Cell 382; G Stacey, J Crook et al., 'Banking Human Induced Pluripotent Stem Cells: Lessons Learned from Embryonic Stem Cells' (2013) 13 Cell Stem Cell 385.

[43] For more on the dual nature of these challenges and the approach adopted to solving them within EBiSC, see S Harmon, 'Standard-Setting for Regenerative Medicine Research: The Case for the European Bank for Induced Pluripotent Stem Cells (EBiSC)' in J Graham and C Holmes (eds.), *Articulating Standards: Translating the Practices of Standardizing Health Technologies*, forthcoming from UBC Press.

to derive cell lines on an individual or project-basis. A failure to manage these operational challenges well will undermine the 'responsibility' that can be attributed to the project. In the biobank context, key operational challenges are 'inclusion', 'traceability', 'distribution', and 'capacity-building'.[44]

The first operational challenge is inclusion of materials into the bank, which is linked to recruitment of donors and consent. It demands that the bank custodian ensures the provenance of the biological sample and associated data. EBiSC must therefore satisfy itself that the deposited sample was taken with consent appropriate to the use intended by the bank, and in compliance with regulatory standards in effect at the place of taking. In short, there must be evidence that those entitled to seek and give consent have acted as expected, and that the recruiter has received prior ethical and scientific approval, which includes an assurance that it is compliant with its local licensing and/or regulatory requirements with respect to tissue-handling and use rules. Additionally, EBiSC must articulate rigorous (scientific) selection criteria for making inclusion decisions with respect to samples meant to be expanded into lines, thereby ensuring that all products distributed are of suitable and documented scientific quality.

Given these demands, EBiSC has developed a Common Consent Form (CCF) to be used by its iPSC Centres in their recruitment activities, which form was developed iteratively with input from beyond the network. Cognizant of the longstanding complaints about human research consent forms,[45] efforts were made to ensure brevity and clarity within the context of a broad consent model (see Declaration 7). Such a model was felt to be in keeping with common practice, and the sustainability needs of the undertaking. The elements of the CCF are identified in Table 1 below. Where donors have voluntarily affirmed the declarations noted therein, EBiSC can be satisfied with the provenance of the material. Of course, caution is warranted; EBiSC cannot guarantee that potential donors have complete understanding, particularly given that it is once-removed from the donors, who are recruited by the iPSC Centres and their extended networks (though these members have received training around conveying the nature and ambitions of EBiSC, assessing understanding, and fielding questions).[46] Nonetheless, until some data is generated as a result of usage, it is impossible to say what potential donors think they are consenting to. As an aspect of its standard-setting agenda, EBiSC expects that the CCF may be taken up by other recruiters, but to justify this, it is probably incumbent on EBiSC (or rather its Legacy Entity) to check-in with donors with respect to their ongoing understanding and expectations.[47]

Table 1: Common Consent Form	
1.	I confirm that I have read, considered, and understood the [*Recruiter*] Information Sheet dated … and the CIP dated ...
2.	I have had the opportunity to ask questions, and have had them answered to my satisfaction.
3.	My donation is voluntarily given.

[44] Stacey et al., note 42; H Gottweiss and G Lauss, 'Biobank Governance in the Post-Genomic Age' (2010) 7 Personalized Medicine 187-195; J Kaye, 'From single biobanks to international networks: Developing e-governance' (2011) 130 Human Genetics 377-382.

[45] See I Albalan, M Doyle et al., 'The Evolution of Consent Forms for Research: A Quarter Century of Changes' (2010) 32 Ethics & Human Res 7, and M Paasche-Orlow, H Taylor et al., 'Readability Standards for Informed-Consent Forms as Compared with Actual Readability' (2003) 348 N Engl J Med 721.

[46] On this point, see B Palmer, E Cassidy et al., 'Effective Use of Consent Forms and Interactive Questions in the Consent Process' (2008) 30 Ethics & Human Res 8.

[47] In this regard, it might be observed that the commercial nature of EBiSC is not emphasised by the declarations in Table 1. While, the commercial nature of EBiSC, together with its sustainability ambitions, are made clear in the Common Information Pamphlet (CIP), commercial use and exploitation is one of the primary concerns of research and biobank participants. As such, one might question whether EBiSC has done enough in these publicly-facing documents to ensure that potential donors understand the implications of their participation. It should also be acknowledged that feedback of information, which is refused in Declaration 8, remains a live issue, and any change to researchers' obligations that might be mandated by law would have to be reflected in a revised CCF and CIP. For more on this, see R Brownsword, 'New Genetic Tests, New Research Findings: Do Patients and Participants have a Right to Know – and Do They have a Right Not to Know?' (2016) 8 Law Innovation Tech 247.

4.	I understand and agree that material and information derived from the samples I donate may be stored indefinitely, and made available to researchers around the world.
5.	I agree that DNA, full genome sequencing data, and other genetic information originating in the samples may be collected, stored and made available to researchers.
6.	I give permission for health professionals to make relevant portions of my medical records available to researchers.
7.	I understand that any samples I donate, and material and information derived from them, may be used in future research, without any need for further consent by me.
8.	I understand that unless required by national law, no information gained from tests conducted on the donated samples, or on iPS cells derived from them, will be communicated to me.
9.	I understand that I will receive no financial gain, research results, health benefit, or any other immediate benefit, as a consequence of my donation of tissue.
10.	I understand that I am free to withdraw from the project at any time, and that withdrawal means: (a) any iPS cells that have already been created from the donated samples will not be destroyed, and information about them will be retained; (b) any original donated samples that are stored, or any portion of them that has not been consumed, will be returned or destroyed at my request; (c) information that I have provided, or that with my consent has been obtained from my medical records, will be deleted and not used for research or any other purpose; (d) I retract my consent to any future access to my records.
11.	I agree to give samples of my blood or other tissue to [*iPSC Centre*].
12.	I [*am / am not*] willing to be re-contacted at any time in the future in connection with this or any other such project.

EBiSC has also developed a Material Deposit Agreement (MDA), which addresses both provenance and quality, touching on some technical matters. Under the MDA, depositors explicitly agree to:

- supply the stipulated quantity of original material to EBiSC;
- provide the original data associated with the material after having taken measures to ensure no personal identifiable information or keys to same are transferred;
- provide evidence that (a) the material was generated in accordance with all necessary licences from applicable authorities, and (b) all necessary and appropriate consents and ethical approvals in relation to the material are in place, or, if no specific consent has been obtained, that approval of inclusion in an international bank such as EBiSC has been granted by a Research Ethics Committee;
- provide information relating to any obligations to third parties in relation to the material;
- comply with all deposit procedures, which include completion of the standard EBiSC Biohazard Risk Assessment form, and documentation necessary to satisfy health and safety regulatory requirements.

For its part, EBiSC agrees to: store the material in accordance with international banking standards;[48] only grant access to the material pursuant to its AUA; implement a communications strategy with potential users;

[48] These standards are articulated in part by the OECD Guidelines on Human Biobanks and Genetic Research Databases (2009), and the evolving state-of-the-art as found in leading scientific publications. The Agreement, as amended on 1 January 2015, stipulates: 4.5 Each Participant represents and warrants that any Human Samples required for use in the Project to be obtained, handled or used by it will be obtained handled or used in accordance with all relevant laws and regulations (including national laws and where applicable local ethical guidelines) regarding the collection, use, transport and subsequent disposal of human tissue or biological samples and that any ethics committee approvals and donor informed consents required will be obtained prior to the commencement of the respective part of the Project work. 4.6 Unless otherwise required or prohibited by law, the Participants warrant, to the best of their knowledge, that in relation to the performance of this Project Agreement: (a) they provide a safe and healthy workplace … ; (b) they do not discriminate against any employees on any ground … [and] they are responsible for controlling their own supply chain and that they shall encourage compliance with ethical standards and human rights by any subsequent supply of goods and services that are used by the Participants when performing their obligations under this Project Agreement.

acknowledge the role of depositors, and note the source of material/data used in publications; comply with legal or regulatory requirements relating to the material and data;[49] and draft an accurate catalogue description of resultant iPSC lines. Once material is received, EBiSC puts it through quality control measures agreed within the Consortium and confirmed by its Scientific Advisory Board.[50] (The physical material is also expanded and characterised at the EBiSC facilities using the most recent reliable techniques.) Through these forms and practices, EBiSC has taken reasonable steps to erect rigorous criteria, both scientific and ethical, for inclusion of lines in the bank.

The second operational challenge is 'traceability', which implicates linkage, enclosure and the ethically significant concept of privacy. Linkage refers to the need for good evidence around the origin of the sample, the cell-line preparation protocol, and the cell-line storage/maintenance regime. This demands good SOPs directed at minimising (or eliminating) the possibility of misidentification as materials come into the bank, and as lines are sent out; it has been noted that "[t]he circulation of poor-quality, misidentified, or mycoplasma-infected cell lines would sustain an unacceptable waste of resources and publication of misleading information."[51] Enclosure refers to the need to protect the privacy of donors, which is guaranteed by Article 8 of the European Convention on Human Rights.[52] It demands compliance with relevant data management/protection rules aimed at preserving confidentiality of the personal and sensitive information associated with samples and related data.[53]

Many aspects of this issue are addressed by the MDA, which requires clear evidence from the depositor as noted above. To protect confidentiality, EBiSC allocates a code to individual samples and records, keeping all personal details of the donor separate from samples, cell-lines and data, but linked by that code. Researchers do not have access to the personal details, and all information is held in secure databases, again in conformity with current international best practice. Reports or publications are also encoded to avoid situations in which the donor's identity might inadvertently be revealed. It is made clear to all donors, however, through the pre-consent CIP, that it is impossible to guarantee that one's identity will not be traceable through other public data systems.[54] It is stipulated, though, that insurance companies and employers will not have access to any information held by the bank, and that access by the police will not be granted other than under court order. Under the MDA, both EBiSC and its depositors agree not to disclose any confidential information which is not original data provided to it by the other. Under the Access and User Agreement (AUA), users confirm that they will make no attempt to establish the personal identity of individual donors from which lines are derived, and they will use banked material or data solely for research and in compliance with all applicable laws, regulations and codes, and third party obligations.

The third operational issue is distribution. Clear and fair rules are needed, not only to gate-keep

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49 Given that the primary EBiSC facility is in the UK, it will have to comply with tissue-handling standards derived from the *Human Tissue Act 2004*, as amended, and its license thereunder, as well as to relevant data-management practices imposed under the *Data Protection Act 1998*, which will be amended in keeping with the new EU General Data Protection Regulation, coming into force in 2018.

50 The criteria for which were negotiated and tested within the Consortium: Harmon, note 43.

51 Stacey et al., note 42, at 387.

52 Article 8(1) Everyone has the right to respect for his private and family life, his home and his correspondence. Article 8(2) There shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic wellbeing of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others.

53 These rules will change in 2018 with the EU General Data Protection Regulation. For more on its implications for biobanks, see M Morrison, J Bell, S Harmon et al., 'The European General Data Protection Regulation: Challenges and Considerations for iPSC Researchers and Biobanks' (2017) 12 Regen Med 693.

54 ICTs are such that genetic identity between the donor cells and the iPSC line can, with some effort, be traced, not least because of the possibility of reprogramming iPSCs back to their origins such that identification of individuals is a possibility: K Aalto-Setälä, B Conklin, B Lo, 'Obtaining consent for future research with induced pluripotent cells: Opportunities and challenges' (2009) 7 PLoS Biology e42; B Lo, L Parham et al., 'Cloning mice and men: Prohibiting the use of iPS cells for human reproductive cloning' (2010) 6 Cell Stem Cell 1.

access to the resource, but to promote the resource and thereby realise its social value. At base, the custodian must ensure that only legitimate researchers with appropriate prior scientific review and ethical approval gain access to the resource, but that they can do so readily and cost-effectively. Rules need to be standardised for particular types of users, and it has been recommended that material transfer agreements should encourage full use of the resource (i.e., refrain from applying serious constraints on research, or from establishing reach-through ownership of discoveries on the part of the derivation centre or the bank). EBiSC promotes its resource through its website and a range of other media. Its AUA states that banked material and data can only be used for research purposes, which includes pre-clinical research and development activities, activities relating to developing the ability to commercialise a drug substance (including process development work), and all activities relating to seeking, obtaining and/or maintaining any regulatory approvals from a regulatory authority. The definition of research purposes excludes the use of material in human clinical testing and as therapeutics. The AUA grants the user and any affiliated entity a non-exclusive, royalty-free, worldwide licence to use the material and data for research during the term of the agreement, subject to third party obligations. It also stipulates that the user retains ownership of any intellectual property arising out of its research reliant on the material and data and derivatives. Upon termination or expiry of the AUA, the user's access rights cease, and the user must discontinue its use of the material, return or destroy any remaining material, and notify each affiliated entity or subcontractor to whom it has given access to the material of the termination or expiry of the AUA. Absent from the AUA is a warranty on the part of the user that it has scientific and ethical review and approval for the research it intends to conduct, or any statement as to the social value of its intended research.

The final operational issue relates to capacity-building (i.e., the development of institutional, organisational, managerial, technological, cultural, and individual skills and knowledge). An entity can only develop and innovate if its workforce is properly trained and given opportunities to cross-fertilise their skills and knowledge through ongoing training and collaboration.[55] EBiSC has undertaken a programme of technical training and information-sharing across the Consortium so that its scientific members (in particular) are using best practice and technologies in their respective activities. Indeed, an entire Work Package is detailed to providing training, and some of the tasks associated with other Work Packages involve identifying and embedding new technologies and establishing systems which will ensure the highest level of quality control. The process has been supplemented by engagement between scientific members and potential depositors. For example, EBiSC has undertaken a number of engagement activities that put EBiSC management and facilities personnel together with iPSC Centres, clinical partners (recruiters), and potential users. At these workshops, stakeholders discuss (1) the manner in which donated tissue and associated medical data will be used to create iPSC lines and to pursue further research, (2) any concerns the stakeholders or their patients may have with the use of donated tissue and data, and (3) national laws and regulations which may impact on the sourcing of tissue/data/lines from that jurisdiction.

All told, ethical governance is intimately connected to practical/scientific operations. In an effort to achieve ethical governance, and to ensure smooth operations, EBiSC has expended significant time and resources to develop sensible and ethically-sensitive SOPS and forms in its Phase I activities. They are not perfect, nor can they be viewed as settled, but they probably represent a more robust compliance with this RRI-alignment criterion than has been achieved under the first one. Making its operational forms (e.g., CIP, CCF, MDA and AUA) more publicly accessible would go some way to improving the situation under the first RRI-alignment criterion.[56]

iii. Duties, Accountability, Reflection and Anticipation

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[55] T Nchinda, 'Research Capacity Strengthening in the South' (2002) 54 Soc Sci Med 1699; A Farazmand, 'Innovation in Strategic Human Resource Management: Building Capacity in the Age of Globalization' (2004) 4 Public Org Rev 3.

[56] Indeed, exposing them and soliciting public feedback on these forms would help to generate a better understanding of the concerns highlighted in note 47 above, an objective undeniably supportive of RRI.

This last RRI-alignment criterion addresses the governance or decision-making framework applicable to the resource (i.e., the powers, liabilities and activities of the bank's custodian as opposed to the documents that structure its relations with depositors and users). RRI imposes both transparency and comprehensibility around the constitution of the bank and how it might be altered in the future. It therefore demands clarity around:

- the constituent bodies and function-specific decision-makers (i.e., lines of responsibility for accepting deposits, setting technical custodial standards, permitting access to the resource);
- the recording/reporting of decisions, processes for review/appeal, and consequences for decisions taken without proper evidence or with improper motivation; and
- the processes for and scope of engagement and reflection (i.e., mechanisms by which the bank can assess its practices, and through which it might develop further information about its functioning).

As noted above, the EBiSC Agreement and DOW serve as the primary governance framework for Phase I. These were negotiated by the Consortium Members with input from the IMI and EFPIA, and they address a host of issues, including management, finances, participant liabilities, ownership of intellectual property, bank usage rights, and more. Under them, EBiSC is comprised of research organisations, universities, small and medium enterprises, and pharmaceutical companies structured as follows:

- Management: The Project Coordination Team (PCT), which is drawn from Roslin Cells and an EFPIA Partner, coordinates the project and manages the emerging entity with support from the Project Administration Office, which is provided by ARTTIC.

- EFPIA Group: Six pharmaceutical companies contribute funds and in-kind support to the project, with support including scientific and business advice/experience.

- iPSC Centres: Eight centres from academia, small enterprise and the not-for-profit sector, each with an established track record in the generation of new iPSC lines, and each with direct connections to European clinical and patient groups, undertake donor recruitment and sample collection in Belgium, Denmark, Germany, Spain, and the UK.

- iPSC Facilities: The main quality assurance and line-derivation facility, operated by Roslin Cells, is at the Babraham Research Campus, England, with a mirror facility at Fraunhofer IBMT, Germany, the latter of which is also developing improved SC culture and cryopreservation systems.

- Scientific Group: Members are designing standardised, high quality, cost effective and rapid scientific characterisation data for the banked iPSC lines, and the European Cell Culture Collection (ECACC), a part of Public Health England, is storing distributable iPSC lines, processing orders via its e-commerce platform, and coordinating cell line distribution.

- IT Group: Members are iteratively designing an information management system which allows users to submit, search and retrieve a rich collection of data on each banked line.

- Legal and Ethics Group: Members are working to facilitate ethical operation and governance that will optimise the utility and longevity of EBiSC.

This represents a dispersed coalition of technical and ethical experts dedicated to recruiting donors from multiple jurisdictions (with the number of depositing jurisdictions expected to increase), and delivering products worldwide. All Work Packages have specified duties in pursuit of this, and it is the responsibility of the Project Coordination Team (PCT), supported by a Project Administration Office located at ARTTIC, to

manage the members toward fulfilment of their deliverables.[57]

However, while these groups are identified on the EBiSC webpage, very little of EBiSC's decisional or power structure, SOPs, or forms are discernible through this portal. The Contact page identifies key decision-makers, but no obvious hierarchy or decision tree. A potential donor or user might therefore have unanswered questions like:

- What decisions does the Consortium Board have responsibility for, and what values will it bring to bear in making decisions (about, for example, dispersing funds, or accepting depositor material)?
- How will the Consortium Board, or, alternatively, the Project Coordinator or the Managing Entity, assess the quality and ethical foundation of a potential user's use of the resource?
- Who is entitled to decide to change EBiSC's decision-making approaches?
- If a patently bad decision is made, who is accountable and to what consequence?

In addition, one could argue that, while EBiSC has made a commitment to support only good and ethical research, it has not clearly signalled to publics the specifics of what is expected or the rigour by which evidence will be scrutinised. Ultimately, then, there is precious little evidence by which the outside observer might evaluate EBiSC with respect to the trust and justice concerns that underlie RRI.[58]

As persistently reiterated above, reflexivity sits at the heart of RRI; this allows for experiential evolution of the bank, its structures, and its practices, thereby supporting responsiveness to changing circumstances. It has been said that reflexive governance:

> … is both about in-parallel partnership in governance in the face of future uncertainty and the facilitation of mutual learning for experience over time. It can be seen as '… a mode of steering that encourages actors to scrutinise and reconsider their underlying assumptions, institutional arrangements and practices.'[59]

In all cases, these characteristics must be relayed and accessible to those within the bank, to those with whom the bank has direct dealings, and to the wider world. Shortcomings in communication are highlighted above, but are compounded when it comes to the specifics of ongoing interactions. EBiSC has done quite well with respect to its internal communications, which rely on an EBiSC newsletter to all members, regular

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[57] A particularly challenging period for the PCT was the 18-month period of EBiSC's formation and launch and 'hot start', a consequence of which was that tasks which one might have expected to have been pursued linearly were in fact developing coincidentally. For example, the preparation of regulatory and ethical maps of Europe, beginning with the partner countries, which would have been most impactful at commencement (or shortly thereafter), were instead prepared over the course of Phase I; a delivery date enforced by the combination of EBiSC's structure and funding, and the need to ensure that all valuable tasks were performed with appropriate competence and diligence. While the pressures of this were felt most sharply by the PCT, all Work Packages had to respond; the Law and Ethics WP faced particular demands as it performed the solicitor-like function of drafting, in dialogue with Consortium members, the CIF, CCF, MDA, and AUAs.

[58] Internally, EBiSC has formulated SOPs to encourage standardised interaction and reliance on common information that will lead to fair decisions applicable to members. For example, EBiSC has formalised a procedure for commissioning new iPSC lines for its inventory. Its Budget Allocation Procedure is triggered in response to applications by members to the Consortium Board for funds to generate new lines, and it relies on pre-defined evaluative criteria. The criteria includes, inter alia, questions around scientific and technological relevance, appropriate expertise, and legal/ethical compliance. The legal/ethical questions include: Is there evidence of relevant legal agreements in place? Is there evidence of informed consent which allows for commercial research associated with the samples? Is there freedom to operate as regards IPR aspects to the lines proposed? Has there been an acceptance of use of EBiSC MDA/AUA? Is any clarification needed with regard to any restrictions or obligations in conjunction with funding from other parties impacting the use of lines?

[59] G Laurie, 'Reflexive Governance in Biobanking: On the value of policy led approaches and the need to recognise the limits of law' (2011) 130 Hum Genet 347, at 351.

Work Package Leader meetings, and the critically important General Assembly Meetings, to which funders and others are invited. In short, EBiSC has established a series of platforms through which it can exercise internal reflexivity (i.e., through which it can collect experiential evidence from its members and collate that into something that can be discussed at multiple levels). This is facilitated by the availability of the Scientific Advisory Board and Ethics Advisory Board to field inquiries on an ad hoc basis. EBiSC is also in constant contact with potential users so as to identify the types of cell lines that the bank should be developing, and it deployed a web-based questionnaire to facilitate such information-gathering. However, with respect to broader and inclusive (external) engagement, EBiSC has not yet taken measures to exemplify a step-increase in standards applicable to international good governance best practice. More will need to be done to facilitate public engagement.

iv. EBiSC and the RRI Criteria Summed Up

What can one conclude from the above assessment of EBiSC's Phase I activities? Certainly, it has achieved a lot, and, one can see that it has been sensitive to the need for ethically-grounded governance processes and forms. It has also gone to some lengths to engage proactively and persistently across the Consortium, and with its primary external (expert) stakeholders. Nonetheless, EBiSC's Phase I achievements are probably best characterised as representing uneven and imperfect compliance with the project-level RRI criteria identified in Section 3 above.

Most significantly, its website – which represents its main public communication tool – is neither complete nor dynamic. With respect to the former, it does not contain a clear and explicit ethical justification of its aims. Thus, it has probably not sufficiently conveyed its social utility, or the 'good outcomes' it is intending to achieve. Additionally, it fails to provide public versions of the key governing instruments (i.e., the Agreement, DOW, CIP, CCF, MDA and AUA), which means that people cannot easily know or assess its structures and decision-making processes. With respect to the latter, dynamism, it caters to depositors and users, but fails entirely to provide a means for subsequent donor contact or public engagement. There are no means by which to open a discourse, to explore issues contained in the CCF, or to air concerns about the commercial elements of the undertaking. Presumably any concerns about such would have been assuaged at the stage of consent (in order to secure participation), but processes for re-engagement might be warranted, and they do not yet exist.[60]

Of course, imperfect reflection of RRI at this stage might be expected; Phase I was always seen as a 'bedding in' period during which conversations across the Consortium would lead to the design, in Phase II, of the Legacy Entity, which would be governed outside the Agreement and DOW. It is at that stage that the bank might expect to be more stringently assessed against the RRI criteria. In short, the largely un-publicised structure that currently exists is not expected to endure unaltered into the Legacy Entity. This begs the question: What follows?

5. RRI and EBiSC Phase II: What Way Forward?

While the above 'what follows' question will be tackled in EBiSC Phase II, the members of the PCT and the Law and Ethics WP, in conversation with other Members, have turned their minds to this creative task. Identifying future governance objectives and forms for the Legacy Entity must take into account how EBiSc will consider the risks of research which it supports, how EBiSC will cooperate with stakeholders, and how it will expose itself to independent scrutiny and critique.[61]

While much biobank operational guidance is grounded firmly in the concept of 'risk', risks to biobank donors, depositors, and users are rather small, and of a different nature and degree than that associated

[60] A more dynamic and interactive platform was recommended at the outset, but was ultimately abandoned as exceeding the budgetary allocation for the non-scientific activities.

[61] Stahl, note 17. It must be acknowledged that RRI presents a design challenge that is empirical: J Gardner and C Wiliams, 'Responsible Research and Innovation: A Manifesto for Empirical Ethics?' (2015) 10 Clinical Ethics 5.

with traditional clinical research. Personal data release and physical damage are examples of risks, but the degree of physical harm is low-to-nil, and the harm from data-release is medium-to-low, depending on the specific context.[62] Thus, it has been argued that a solidarity-based approach (as opposed to a strongly risk and autonomy-based approach) to biobank governance is warranted,[63] and that:

> A biobank reflective of [solidarity] would pursue assisting others as its main research goal; that is, the main activity of the biobank would always have to be research aiming to improve health of individuals or populations (or comparable, other-directed goals). In addition, transparency towards participants is required about how the goal of improving the health of individuals and populations relates to commercial goals.[64]

At present, and consistent with other biobanks, EBiSC has focused on risk and adopted a broad consent model, with limitations relating to withdrawal. Given the above, an evolution might be warranted, though again, it would need to be extensively discussed within and beyond the Consortium. To date three interrelated governance objectives have been raised within EBiSC, at least preliminarily: 'alignment'; 'experiential design'; and 'transparency'.

Alignment refers to the ambition of having EBiSC's practical goals reflected in its (future) governance structure. Some of those practical goals include: (1) the inspiration and preservation of public trust, which necessitates ongoing attention to operational issues such as provenance of material, harmonisation of standards and practices, and transparency of decision-making and expectations around use; and (2) innovative approaches to sustainability and accessibility, which necessitates a sound business model, minimal barriers to use, and reduced encumbrances on cell-lines made available through the bank. The second objective – experiential design – relates directly to reflexivity as articulated in Section 3 above. The expectation is that EBiSC will develop evidence around its functioning and draw on the expertise that its members have to formulate solutions in a responsive way to operational demands/needs. Of course, moving forward, this will demand a built-in mechanism so that incremental change can be realised. This, in turn, requires that governance structures/mechanisms are proportionate (as opposed to burdensome) and are applicable to all members. The final governance objective is that of transparency. Depositors, users, and publics should have clear and unambiguous information not only about the cell-lines in the resource, but also about how decisions are made, and by whom. One can see, then, that some of the existing shortcomings (from an RRI perspective) are already being discussed.

I contend that these objectives impose on EBiSC two associated duties. The first, and one that has been advocated elsewhere,[65] is to agree on a set of values that will form a backdrop to EBiSC. They serve as a signal to stakeholders and publics about what will inform actions and decisions. The second is to adopt an Ethics and Governance Framework (EGF) that publics can access, understand, and use as a benchmark to assess the Legacy Entity.

Given EBiSC's ambition to advance socially valuable scientific outcomes, and good science and corporate citizenship, a range of values seems pertinent. Empirical research in the regenerative medicine setting has already uncovered a number of values in three broad categories (i.e., values that inform the researcher's social vision and outcomes; values that inform the project's approach to governance; values

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62 European Commission Expert Group on Dealing with Ethical and Regulatory Challenges of International Biobank Research, *Biobanks for Europe: A Challenge for Governance* (Brussels: EC, 2012). And the risk of improper data release will be further minimised as actors take steps to comply with the new General Data Protection Regulation 2018.

63 S Harmon and A McMahon, 'Banking (on) the Brain: From Consent to Authorisation and the Transformative Potential of Solidarity' (2014) 22 Med Law Rev 572.

64 B Prainsack and A Buyx, 'A Solidarity-Based Approach to the Governance of Research Biobanks' (2013) 21 Med Law Rev 71, at 77.

65 Ibid, at 84.

that resource operators expect users to hold and advance).[66] Obviously, these categories are not watertight, and values relevant to one category may be relevant others.

With respect to values applicable to social vision, and the development and provision of service, the notions of 'wellbeing', 'solidarity', 'dignity', 'justice', and 'autonomy' are all important. On wellbeing, EBiSC must acknowledge that community wellbeing and productivity depends on human health; it is important to protect life, health, and wellness, both physical and psychological, and to support actions which facilitate quality of life. On solidarity, EBiSC must recognise the importance of interconnectedness, emotional ties to others, and the common good, and assume a general obligation to advance the wellbeing of the vulnerable. The value of research is therefore often sensibly measured by how well it aligns with society's problems and generates social benefits, an idea at the heart of RRI. On dignity, EBiSC must recognise the importance of respecting people; thus, while it properly espouses the value of knowledge generated within moral bounds, and the associated propriety of pushing boundaries and being creative, it must acknowledge the need to balance the research imperative with other values, always being careful not to instrumentalise people. On justice, EBiSC must realise equality and equity through its operation, acknowledging the need to share fairly the benefits of research. On autonomy, EBiSC must understand the desire of individuals and communities to exercise free will, and so create space for people to make decisions about themselves and for themselves, according to their values. This not only demands that stakeholders be given adequate information so they can weigh options and make reasonably informed decisions, and be satisfied that agents will take reasonable steps to protect their personal information, but also empowering them, and work around dynamic consent may be useful here.[67]

With respect to values that inform approaches to governance of the resource, 'transparency', 'engagement' and 'reflexivity' are important, and are highlighted by RRI. Adherence to these values combined suggests that EBiSC must aim to model comprehensible and open decision-making structures, and to encourage information-sharing in multiple directions by designing rational structures to manage the resource, multi-directional communication strategies, and undertake periodic reviews of its governance practices to ensure that they are fit for purpose. Engagement emphasises the function of partnership and information-sharing across multiple communities, while reflexivity emphasises the need for governance practices and strategies to evolve through iterative review, taking into account the views and experiences of its members and stakeholders.

Finally, with respect to values that depositors and users might be expected to advance, many of those identified above are again implicated. But to them one might add 'integrity', 'excellence', and 'safety'. This means that EBiSC will have to take steps to ensure that the researchers with whom it interacts are honest with and about patients and subjects, and with research data, and that they must sensitively balance the responsibility of advancing human knowledge with that of benefitting humankind, and ensuring that donors and patients are not put at undue risk.

Many of these values are implicated by the notion of RRI, and many of them are already advanced by EBiSC through its processes and operations (and its initial attempt to meet the RRI criteria). But by explicitly naming and highlighting these values, EBiSC would signal its commitment to supporting only virtuous researchers conducting research with some potential to alleviate human suffering. Operationalising these values implicates the second duty noted above – designing a suitable EGF that facilitates sustainability. The EGF could erect structures and processes that are clearly consistent with, and explicitly targeted at,

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[66] See S Harmon, 'Regulation of Stem Cell and Regenerative Science: Stakeholder Opinions, Plurality and Actor Space in the Argentine Social/Science Setting' (2010) 2 Law, Innovation & Technology 95, and S Harmon, *Opinion 4:2010: Guiding Values: Argentine Stem Cell Research and Regenerative Medicine*, for the Argentine Ministry of Science & Technology, at http://www.scriptcentre.ed.ac.uk/opinions.

[67] K Steinsbekk, B Myskja and B Solberg, 'Broad consent versus dynamic consent in biobank research: Is passive participation an ethical problem?' (2013) 21 European J Human Genetics 897; D Stein and S Terry, 'Reforming biobank consent policy: a necessary move away from broad consent toward dynamic consent' (2013) 17 Genetic Testing and Molecular Biomarkers 855; J Kaye, E Whitley et al., 'Dynamic Consent: A patient interface for twenty-first century research networks' (2015) 23 European J Human Genetics 141.

these values. Some of the specific matters that an EGF would address are outlined above (i.e., constituent bodies, decisional authority, communication strategy and platform, structures and practices supportive of engagement, etc.), but the interaction between research and commerce, access by commercial entities, and the need for the biobank itself to be sustainable would all have to be explicitly addressed.

6. Conclusions

Good governance is enacted by many parties, including those who are themselves governed. Thus biobank operators who are subject to external regulation also construct the governance setting applicable to them. In Europe, the good governance of research and innovation is presently influenced by the regulatory notion of RRI, a notion which has implications not only for regulators (and funders), but also for research institutions and researchers – regulatees. Although the majority of existing and emerging biobanks *fail* to adopt a prospective governance strategy,[68] the obligations imposed by RRI (which itself is surely tied to the ideas of legitimacy and transparency) make clear that this is not an acceptable state of affairs. The regulatory expectation is that actors will be communicative, undertakings will be structured to ensure the ethicality of their operations, and decisions will be evidence-based, informed by dialogue, and anticipatory in scope. Given EBiSC's multiple ambitions (one of which is to serve as a flagship enterprise and standard-setter for Europe and beyond), it is incumbent on EBiSC to design in Phase II a governance framework that is robustly supportive of RRI (i.e., comprehensible, reflective of the above values and justice characteristics, and conveyed to the public in an accessible manner). This must be achieved in the face of changing legal standards and must not impose undue burdens on those trying to advance knowledge (i.e., depositors to and users of the resource). This is by no means an easy task. Presumably, the not-for-profit Legacy Entity will be structured like a corporation, but, as is well recognised in the life sciences and public resource setting, something more than a straight-up corporate structure is warranted if justifiable trust is to be maintained.[69] Attention must be paid to the 'stewardship' role of the body. EBiSC Phase I has represented a sound if imperfect launch-pad, but important work lies ahead in Phase II if EBiSC is to meet the promises made through its founding.

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[68] A Cambon-Thompson, E Rial-Sebbag and B Knoppers, 'Trends in Ethical and Legal Frameworks for the use of Human Biobanks' (2007) 30 Euro Respiratory J 373; R Isasi and B Knoppers, 'From Banking to International Governance: Fostering Innovation in Stem Cell Research' (2011) Stem Cell International Online ID498132.

[69] In this regard, note the experience of UK Biobank, which relies on a well-articulated EGF and an independent Ethics and Governance Council to comment on and engage with the scientific undertaking: see http://egcukbiobank.org.uk/ [accessed 24 September 2015]. While there has been much discussion about how to update UK Biobank structures, the value of some constituting document and established processes for engagement and anticipation cannot be denied.